



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/601,140	06/20/2003	Sakari Kauppinen	57764 (71994)	6647

21874 7590 02/16/2007
EDWARDS & ANGELL, LLP
P.O. BOX 55874
BOSTON, MA 02205

EXAMINER

CROW, ROBERT THOMAS

ART UNIT	PAPER NUMBER
----------	--------------

1634

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/16/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary

Application No.

10/601,140

Applicant(s)

KAUPPINEN ET AL.

Examiner

Robert T. Crow

Art Unit

1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 30 November 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-9, 13-23, 25-80, 90-93, 110-119, 127-137, 139 and 140 is/are pending in the application.
- 4a) Of the above claim(s) 23 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-9, 13-22, 25-80, 90-93, 110-119, 127-137, 139 and 140 is/are rejected.
- 7) ☒ Claim(s) 7, 55, 58, 64, and 110 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- 1: ☐ Certified copies of the priority documents have been received.
- 2: ☐ Certified copies of the priority documents have been received in Application No. _____.
- 3: ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 7/2006.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____.

Art Unit: 1634

FINAL ACTION

Status of the Claims

1. This action is in response to papers filed 30 November 2006 in which claims 1-3, 9, 13-15, 17, 22, 25-26, 28, 31-34, 37-38, 42-43, 45-47, 55, 58, 92-93, 110-119, 127-and 135 were amended, claims 10-12 and 138 were canceled, and no new claims were added. All of the amendments have been thoroughly reviewed and entered.

Applicant has withdrawn claim 23 for the reasons stated on page 23 of the Remarks filed 30 November 2006.

The previous objections to the specification in the previous Office Action are withdrawn in view of the amendments.

The previous rejections under 35 U.S.C. 112, second paragraph, are withdrawn in view of the amendments.

The previous rejections under 35 U.S.C. 102(b) and 35 U.S.C. 103(a) not reiterated below are withdrawn in view of the amendments. Applicant's arguments have been thoroughly reviewed and are addressed following the rejections necessitated by the amendments.

Claims 1-9, 13-22, 25-80, 90-93, 110-119, 127-137, and 139-140 are under prosecution.

Interview Summary

2. The Remarks filed 30 November 2006 are incomplete because no summary of the telephonic interview of 8 August 2006 with Stephana Patton is provided.

For the next response to this Office Action to be complete, Applicant is **REQUIRED** to include the substance of the interview. Failure to comply with this requirement will be considered **nonresponsive**. See MPEP § 713.04.

Art Unit: 1634

Information Disclosure Statement

3. The Information Disclosure statement filed 14 July 2006 is acknowledged. However, all of the references have been crossed out because all of the references were previously cited by the examiner and are already on the record.

Claim Objections

4. Claims 7, 55, 58, 64, and 110 are objected to because of the following informalities:

A. Claim 7 has an underlined semicolon in line 4 after the word "length." This semicolon was previously underlined, and is therefore not an amendment.

B. Claim 55 contains the recitation "[[55]]" in line 1 of the claim. The numeral "55" was not present in any of the previous sets of claims.

C. Claim 58 has added the recitation "indicated eukaryotic mRNA in the sample" at the end of the claim. This recitation was not present in the previous claim set and is not underlined. Hence, the amendment is not proper.

D. The period at the end of claim 64 has been underlined; however, the period was present in the previous version of the claims, and is therefore not an amendment.

E. Claim 110 contains the recitation "wherein the oligonucleotide wherein the LNA oligonucleotide comprises" in lines 10-11 of the claim. This appears to be a typographical error.

5. It is emphasized that Applicant's response filed 30 November 2006 has been considered in the interest of customer service and compact prosecution. However, for the response to this Office Action to be complete, Applicant is **REQUIRED** to correct the errors listed above and file amendments that are compliant with 37 CFR 1.121. Failure to comply with this requirement will be considered **nonresponsive**.

Art Unit: 1634

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-9, 13-22, 25-80, 90-93, 110-119, 127-137, and 139-140 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-9, 13-22, 25-80, 90-93, 110-119, 127-137, and 139-140 are indefinite in claims 1-3, 92, and 110, each of which recites the limitation "at least twenty to twenty-five repeating consecutive nucleotides" and the end of claims 1-3, in lines 7-8 of claim 92, and in lines 11-12 of claim 110. It is unclear what the minimum number of repeating consecutive nucleotides is because a range is presented. It is suggested that the claim be amended to recite only a single number as the minimum number of repeating consecutive nucleotides.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the

Art Unit: 1634

examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1-9, 13-17, 22, 27-30, 33-56, 59, 64-67, 73-76, 91-92, 110-113, 118-119, 127-135, and 139 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wengel et al (PCT International Publication No. WO 99/14226, published 25 March 1999) in view of Monforte et al (U.S. Patent No. 6,051,378, issued 18 April 2000) and further in view of Skouv (U.S. Patent No. 6,303,315 B1, issued 16 October 2001).

Regarding claims 1-9, 13-17, 27-30, 33-50, 53-54, 74-76, 91-92, and 127-135, Wengel et al teach a method for detecting an/or isolating a target nucleic acid molecule having a homopolymeric sequence. In a single exemplary embodiment, Wengel et al teach comprising: treating a sample containing nucleic acid molecules with an LNA oligonucleotide to thereby detect and/or isolate a nucleic acid molecule; namely, poly dT primers containing LNA T residues are used to prime cDNA synthesis (page 181, Example 160). Poly dT is a homopolymer, a repetitive element, and a conserved nucleotide sequence. Wengel et al teach the length of the poly dT, which is a repeating sequence, is at least 10 nucleotides long (e.g., Probe RTZ2, 5'- TTT TTT TTT TTT TT3'; page 181, Example 160 and page 30, lines 14-20). Wengel et al also teach the oligonucleotides carry an anthraquinone and a linker on the 5' end (page 62, lines 15-27), that said linker is a higher hexaethylene glycol polymer; namely, polyethylene glycol (page 21, lines 10-15), and that said solid support is a polymer support is a polystyrene bead (page 62, lines 15-18).

UV light is used to immobilize the anthraquinone (Example 149).

The oligo dT LNA of Wengel et al is complementary to a sequence consisting substantially of a poly (A) nucleotide sequence; namely, mRNA has a poly (A) tail (page 181, Example 160). The mRNA also has at least one nucleobase that is different from A; i.e., the message has the start codon AUG, which has bases other than A, which is the homopolymeric nucleic acid sequence. The oligo dT LNA of Wengel binds the poly (A) tail of the mRNA.

Wengel et al further teach the LNA oligonucleotide has at least one base pair difference to a complementary sequence it is designed to detect and/or isolate because the LNA molecules detect end

Art Unit: 1634

mismatches (page 170, example 152), and that the probes include poly repetitive sequences (e.g., Probe RTZ2, 5'- TTT TTT TTT TTT TT3'; page 181, Example 160). The probe RTZ 2 has an LNA residue at the -1 position because the probe binds to targets that place the LNA residues at the -1 position.

Wengel et al teach the probe 5'- TTT TTT TTT TTT TT3' (page 187, Table 1), which has 4 of 14 or 28% of the residues as LNA. Wengel et al also teach the LNA probe comprises a compound of the formula 5'-Y^q-(X^p-Yⁿ)_m-X^pZ-3'; namely, probe RTZ2, 5'- TTT TTT TTT TTT TT3' , where q=0, n=0, the first p = 6, the second p = 3, and Z is a dT residue at the 3' end (page 181, Example 160). This oligo has at least two consecutive LNA molecules (in bold) and has non-modified nucleotides. Wengel et al teach the association constant of the LNA oligonucleotide is higher than the association constant of the complementary strands of a double stranded molecule because LNA has a positive effect on the thermal stability of duplexes towards DNA and RNA (page 151, Example 135), that the association constant of the LNA oligonucleotide is higher than the dissociation constant of the complementary strand in a double stranded molecule because the LNA performs strand displacement on dsDNA (page 59, lines 23-29) and that LNA-modified oligonucleotides function efficiently in the sequence specific capture of RNA molecules (page 182, lines 23-24); thus, the LNA oligonucleotide is complementary to the sequence it is designed to detect and/or isolate.

Wengel et al teach the LNA is a molecular beacon (page 64, lines 1-25), which comprises a fluorophore moiety and a quencher moiety, positioned in such a way that a hybridized state of the oligonucleotide can be distinguished from an unbound state of the oligonucleotide by an increase in the fluorescent signal from the nucleotide.

Wengel et al teach the T_m of 5'- TTT TTT TTT TTT TT3' , is about 50°C (page 187, Table 1), and wherein the LNA oligonucleotide hybridizes to complementary sequences of eukaryotic RNA; namely, the LNA are used to activate genes of therapeutic interest (page 60, lines 21-24), wherein the therapeutic applications are in humans (page 18, lines 5-6).

Art Unit: 1634

Wengel et al further teach the LNA is a molecular beacon, which forms a hairpin in the absence of the target (page 64, lines 1-25), and subsequently brings a quencher molecule in sufficient proximity to a reporter molecule to quench fluorescence of the reporter molecule when the probe is not bound to the target.

Wengel et al teach the LNA oligonucleotide hybridized to complementary sequences of mRNA because the poly dT probes are primers containing LNA T residues are used to prime Arabidopsis mRNA (page 181, Example 160). Wengel et al also teach the LNA probes are used to capture nucleic acids that are then subjected to PCR amplification (page 62, lines 4-10 and page 195, Example 148). Wengel et al also teach selective high stringency binding a low salt concentration (page 183

Wengel et al teach a poly dT LNA primer that is 15 bases long (page 181, lines 15-20), as well as LNA molecules of any lengths of up to 10000, and especially lengths of up to at least 50 nucleotides (page 30, lines 14-20). Wengel et al do not specifically teach oligo dT having a length of at least 20 nucleotides.

However, Monforte et al teach hybridization using capture probes that are 30-50 nucleotides in length with the added advantage that probes having these lengths provide added stability to the hybridization of the capture probe as a result of the length (column 19, lines 40-42).

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method of Wengel et al with oligonucleotides having the lengths as taught by Monforte et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method having detection oligonucleotides with lengths that provide added stability to the capturing LNA oligonucleotide as a result of the length as explicitly taught by Monforte et al (column 19, lines 40-42).

Neither Wengel et al nor Monforte et al teach chaotropic reagents.

However, Skouv teaches the preparation of nucleic acids from biological samples using LNA and lysing in the presence of chaotropic agents (Abstract) with the added advantage that chaotropic agents

Art Unit: 1634

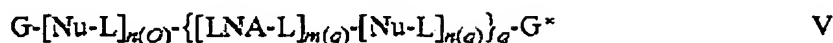
facilitate lysis of the cells (column 1, lines 38-42). Monforte et al further teach the chaotropic agent is guanidinium isothiocyanate, which has the added advantage of inhibiting nucleases (column 4, lines 58-67), which degrade the target to be isolated. Skouv further teaches a concentration of 4M guanidinium has the added benefit of providing a good specificity in binding to the target in a short time (Figure 2-2). Skouv also teaches NaCl concentration between about 0 and 1M, which have the added benefit of controlling stringency (column 4, lines 53-57).

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method of Wengel et al in view of Monforte et al with the chaotropic agent guanidinium isothiocyanate at 4M and NaCl concentration of less than 25 M as taught by Skouv with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in facilitating the lysis of cells, inhibition of target degradation by nucleases, good specificity in the isolation of the target nucleic acid, and controlled stringency of hybridization as explicitly taught by Skouv (column 1, lines 38-42, column 4, lines 58-67, column 4, lines 53-57, and Figure 2-2).

Regarding claims 22 and 25-26, the method of claim 20 is discussed above. While Wengel et al teach the oligonucleotides carry an anthraquinone and a linker on the 5' end (page 62, lines 15-27), that said linker is a higher hexaethylene glycol polymer (i.e., polyethylene glycol; page 21, lines 10-15), and biotinylated LNA (page 19, lines 8-10), neither Wengel et al nor Monforte et al specifically teach LNA at every third residue (i.e., compound 3 [SEQ ID NO. 3]).

However, Skouv teaches an LNA oligomer having the formula (column 23)

Art Unit: 1634



wherein

q is 1-50;

each of $n(0), \dots, n(q)$ is independently 0-10000;

each of $m(1), \dots, m(q)$ is independently 1-10000;

with the proviso that the sum of $n(0), \dots, n(q)$ and $m(1), \dots, m(q)$ is 2-15000;

G designates a 5'-terminal group;

each Nu independently designates a nucleoside selected from naturally occurring nucleosides and nucleoside analogues;

each LNA independently designates a nucleoside analogue;

each L independently designates an internucleoside linkage between two groups selected from Nu and LNA, or L together with G^* designates a 3'-terminal group; and

each LNA-L independently designates a nucleoside analogue of the general formula I as defined above.

which encompasses the alternating pattern of the instant claim, with the added advantage that the oligomers have good affinity and specificity in hybridization (column 24, lines 5-7).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified to method as taught by Wengel et al in view of Monforte et al in view of Skouv with the alternating LNA residues as taught by Skouv with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in good affinity and specificity in hybridization as explicitly taught by Skouv et al (column 24, lines 5-7).

Regarding claim 51 and 52, the method of claim 48 is discussed above. The courts have stated where the claimed ranges "overlap or lie inside the ranged disclosed by the prior art" and even when the

Art Unit: 1634

claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have similar properties, a *prima facie* case of obviousness exists (see *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990); *Titanium Metals Corp. of America v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985) (see MPEP 2144.05.01). Therefore, the claimed temperatures of about 55 °C and about 60 °C are obvious over the temperatures taught by Wengel et al (page 187, Table 1).

Regarding claims 55-56, 59, 64-67, and 139, the method of claim 1 is discussed above. Wengel et al also teach the LNA oligonucleotide is complementary to poly(A) tails in eukaryotic mRNA; namely, poly dT probes are used as primers for Arabidopsis mRNA and contain LNA T0 (page 181, Example 160). The LNA oligonucleotide is synthesized with an anthraquinone moiety and a linker at the 5'-end of said oligonucleotide (page 62, lines 15-27), wherein said linker is a higher hexaethylene glycol polymer; namely, polyethylene glycol (page 21, lines 10-15).

Wengel et al also teach detection with probes using chemiluminescent reporter groups (i.e., labels page 9, lines 1-19 and page 19, lines 8-20), contacting the sample with a polymerase and at least one nucleotide during reverse transcription of the mRNA; page 181, Example 160), and said reaction occurs directly on a surface (page 62, lines 8-10). Wengel et al also teach digoxigenin incorporated into nucleic acid probes; namely, the reporter groups are digoxigenin (page 19, lines 8-10).

While Wengel et al teach LNA oligonucleotides covalently coupled to a solid polymer support (page 15, lines 7-9) via excitation of the anthraquinone moiety using UV light (page 62, lines 23-26 and page 166, Example 149), Wengel et al do not specifically teach immobilization of the poly dT primers.

However, Wengel et al do teach that immobilization of nucleic acids is preferred because it allows hybridization and capture to occur simultaneously (page 62, lines 4-10).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method as taught by Wengel et al in view of Monforte et al and in view of Skouv by immobilizing the LNA molecules as also taught by Wengel with a reasonable

Art Unit: 1634

expectation of success. The ordinary artisan would have been motivated to make the modification because the modification would have resulted in simultaneous hybridization and capture as explicitly taught by Wengel et al (page 62, lines 4-10).

Regarding claim 73, the method of claim 59 is discussed above. While Wengel et al teach the LNA is a primer (page 181, Example 160), Wengel et al do not teach adding an additional primer.

However, Skouv teaches hybridization using LNA capture probes (Abstract) further comprising the addition of two (i.e., additional) primers which has the added advantage allowing ligation of the two primers for an LCR reaction, which allows exponential amplification of the target sequences without relying on individual nucleotides for template extension (column 6, lines 34-47).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method as taught by Wengel et al in view of Monforte et al in view of Skouv with the additional primers as taught Skouv with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because the modification would have resulted in a method that allows exponential amplification of the target sequences without relying on individual nucleotides for template extension as explicitly taught by Skouv (column 6, lines 34-47).

Regarding claims 110-113 and 118-119, Wengel et al teach a method of isolated RNA. In a single exemplary embodiment, Wengel et al teach providing a sample with genomic RNA and contacting said genomic RNA with an LNA capture probe having repeating consecutive nucleotides that is substantially complementary to the consecutively repeating bases in the genomic RNA; namely, poly dT primers containing LNA T residues are used to bind polyadenylated mRNA (page 181, Example 160). Wengel et al teach a poly dT LNA primer that is 15 bases long (page 181, lines 15-20); as well as LNA molecules of any lengths of up to 10000, and especially lengths of up to at least 50 nucleotides (page 30, lines 14-20). Wengel et al do not specifically teach oligo dT having a length of at least 20 nucleotides.

Art Unit: 1634

As stated above, even when the claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have similar properties, a *prima facie* case of obviousness exists. Therefore, the claimed temperatures of about 55 °C and about 60 °C are obvious over the temperatures taught by Wengel et al (page 187, Table 1).

However, Monforte et al teach hybridization using capture probes that are 30-50 nucleotides in length with the added advantage that probes having these lengths provide added stability to the hybridization of the capture probe as a result of the length (column 19, lines 40-42).

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method of Wengel et al with oligonucleotides having the lengths as taught by Monforte et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a method having detection oligonucleotides with lengths that provide added stability to the capturing LNA oligonucleotide as a result of the length as explicitly taught by Monforte et al (column 19, lines 40-42).

Neither Wengel et al nor Monforte et al teach lysing with chaotropic reagents or infectious diseases.

However, Skouv teaches the preparation of nucleic acids from biological samples using LNA and lysing in the presence of chaotropic agents to dissolve the cellular components (Abstract) with the added advantage that chaotropic agents facilitate lysis of the cells (column 1, lines 38-42). Monforte et al further teach the chaotropic agent is guanidinium isothiocyanate, which has the added advantage of inhibiting nucleases (column 4, lines 58-67), which degrade the target to be isolated. Skouv further teaches a concentration of 4M guanidinium has the added benefit of providing a good specificity in binding to the target in a short time (Figure 2-2). Skouv also teaches detection of RNA from an infectious disease for diagnoses with the added advantage of allowing identification of a particular microorganism in a complex biological mixture of nucleic acids (i.e., genotyping) from a patient ; column 3, lines 30-60).

Art Unit: 1634

Skouv also teaches denaturing the sample RNA by heating with the added advantage of removing significant secondary or tertiary structures (column 3, lines 30-60), which improves binding to the LNA probes.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method of Wengel et al in view of Monforte et al with the chaotropic agent guanidinium isothiocyanate at 4M, denaturation, and RNA from infectious diseases as taught by Skouv with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in facilitating the lysis of cells, inhibition of target degradation by nucleases, allowing identification of a particular microorganism in a complex biological mixture of nucleic acids and removing significant secondary or tertiary structures as explicitly taught by Skouv (column 1, lines 38-42, column 4, lines 58-67, Figure 2-2, and column 3, lines 30-60).

8. Claims 18, 20, and 25-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wengel et al (PCT International Publication No. WO 99/14226, published 25 March 1999) in view of Monforte et al (U.S. Patent No. 6,051,378, issued 18 April 2000) in view of Skouv (U.S. Patent No. 6,303,315 B1, issued 16 October 2001) and applied to claim 1 above, and further in view of Takahashi et al (U.S. Patent No. 5,955,072, issued 11 September 1999).

Regarding claims 18, 20, and 25-26, the method of claim 1 is discussed above on pages 4-7. While Wengel et al teach Neither Wengel et al, Monforte et al, nor Skouv teach the LNA is complementary to a sequence that is substantially poly T or poly U; i.e., the sequence of the LNA is poly A.

However, Takahashi et al teach methods comprising poly A and that poly A sequences have the advantage of allowing purification by specific adsorption onto oligo dT columns (column 20, lines 26-33).

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising LNA oligonucleotides of Wengel

Art Unit: 1634

et al in view of Monforte et al in view of Skouv with the poly A oligonucleotides of Takahashi et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in poly A LNA molecules that have the added advantage of allowing purification by specific adsorption onto oligo dT columns as explicitly taught by Takahashi et al (column 20, lines 26-33).

9. Claims 19 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wengel et al (PCT International Publication No. WO 99/14226, published 25 March 1999) in view of Monforte et al (U.S. Patent No. 6,051,378, issued 18 April 2000) in view of Skouv (U.S. Patent No. 6,303,315 B1, issued 16 October 2001) and applied to claim 1 above, and further in view of Scheele (U.S. Patent No. 5,162,209, issued 10 November 1992).

Regarding claims 19 and 21, the method of claim 1 is discussed above on pages 4-7. Neither Wengel et al, Monforte et al, nor Skouv teach the LNA is complementary to a sequence that is substantially either poly G or poly C; i.e., the sequence of the LNA is poly dC or poly dG.

However, Scheele teaches methods comprising sequences of either poly dC or poly dG which have the added advantage hybridization of poly dG and poly dC sequences is more stable than other sequences (column 5, lines 52-57).

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising LNA oligonucleotides of Wengel et al in view of Monforte et al in view of Skouv with the poly dG or poly dC oligonucleotides of Scheele with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in poly dG or poly dC LNA molecules that have the added advantage of increased stability when hybridized as explicitly taught by Scheele (column 5, lines 52-57).

Art Unit: 1634

10. Claims 31-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wengel et al (PCT International Publication No. WO 99/14226, published 25 March 1999) in view of Monforte et al (U.S. Patent No. 6,051,378, issued 18 April 2000) in view of Skouv (U.S. Patent No. 6,303,315 B1, issued 16 October 2001) and applied to claim 1 above, and further in view of Beier et al (Science, vol. 283, pp. 699-703 (1989)).

Regarding claims 31-32, the method of claim 1 is discussed above on pages 4-7. Neither Wengel et al, Monforte et al, nor Skouv teach alpha-L LNA monomers or xylo-LNA monomers,

However, Beier et al teach locked nucleic acids comprising alpha-L LNA monomers and xylo monomers (e.g., Scheme 1) with the added advantage that the monomers are stronger Watson-Crick binders (Abstract).

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising LNA oligonucleotides of Wengel et al in view of Monforte et al in view of Skouv with the monomers of Beier et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in LNA molecules that have the added advantage of Watson-Crick binding as explicitly taught by Beier et al (Abstract).

11. Claim 57 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wengel et al (PCT International Publication No. WO 99/14226, published 25 March 1999) in view of Monforte et al (U.S. Patent No. 6,051,378, issued 18 April 2000) in view of Skouv (U.S. Patent No. 6,303,315 B1, issued 16 October 2001) and applied to claim 56 above, and further in view of Bobrow et al (U.S. Patent No. 5,731,158, issued 24 March 1998).

Regarding claim 57, the method of claim 56 is discussed above on pages 9-10. Neither Wengel et al, Monforte et al, nor Skouv teach tyramide signal amplification.

Art Unit: 1634

However, Bobrow et al teach tyramide signal amplification (column 4, lines 36-49) as a reporter system for nucleic acid binding systems (column 6, lines 49-55) with the added advantage that the reporter system allows quantitation of the presence of the analyte (Abstract).

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising LNA oligonucleotides of Wengel et al in view of Monforte et al in view of Skouv with the tyramide system of Bobrow et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in an reporter group on the LNA molecule that has the added advantage of allowing quantitation of the presence of the analyte as explicitly taught by Bobrow et al (Abstract).

12. Claim 58 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wengel et al (PCT International Publication No. WO 99/14226, published 25 March 1999) in view of Monforte et al (U.S. Patent No. 6,051,378, issued 18 April 2000) in view of Skouv (U.S. Patent No. 6,303,315 B1, issued 16 October 2001) and applied to claim 56 above, and further in view of Nilsen (U.S. Patent No 6,046,038, issued 4 April 2000).

Regarding claim 58, the method of claim 56 is discussed above on pages 9-10. Wengel et al teach eukaryotic cDNA is produced from the eukaryotic mRNA of Arabidopsis using primers containing LNA T residues (page 181, Example 160). Wengel et al also teach detection of excited fluorochromes to indicate the mRNA is in the sample (page 64, lines 1-25). Neither Wengel et al, Monforte et al, or Skouv teach cDNA capture by dendrimers.

However, Nilsen teaches capture of cDNA with labeled target specific dendrimers with the added advantage that the dendrimers allow detection using probes that are only a fraction of the size of the cDNA (column 13-14, Example 4) with an amplified signal (column 9, lines 20-26).

Art Unit: 1634

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising fluorescent LNA oligonucleotides and cDNA of Wengel et al in view of Monforte et al in view of Skouv with the dendrimers of Nilsen with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in detection of eukaryotic mRNA with dendrimers that has the added advantage of allowing probes that are only a fraction of the size of the cDNA that still provide an amplified signal as explicitly taught by Nilsen (column 13-14, Example 4) Abstract).

13. Claims 60-61, 69, and 70, are rejected under 35 U.S.C. 103(a) as being unpatentable over Wengel et al (PCT International Publication No. WO 99/14226, published 25 March 1999) in view of Monforte et al (U.S. Patent No. 6,051,378, issued 18 April 2000) in view of Skouv (U.S. Patent No. 6,303,315 B1, issued 16 October 2001) and applied to claim 59 above, and further in view of Eberwine et al (U.S. Patent No. 5,514,545; issued 7 May 1996).

Regarding claims 60-61, 69, and 70, the method of claim 59 is discussed above on pages 4-7. While Wengel et al teach the LNA is a molecular beacon (page 64, lines 1-25), and thus comprises a fluorophore moiety and a quencher moiety, positioned in such a way that a hybridized state of the oligonucleotide can be distinguished from an unbound state of the oligonucleotide by an increase in the fluorescent signal from the nucleotide that is detected (page 64, lines 1-25), neither Wengel et al, Monforte et al, nor Skouv teach generating a plurality of copies of the eukaryotic mRNA at a constant temperature.

However, Eberwine teaches a method of generating a plurality of copies of mRNA via amplification (column 4, lines 34-55) at a constant temperature (i.e., room temperature; Example 3) with primers (column 3, lines 1-10), which has the added advantage of aiding in the characterization of cell identity (Abstract).

Art Unit: 1634

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method as taught by Wengel et al in view of Monforte et al in view of Skouv with amplification at a constant temperature with primers as taught Eberwine et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because the modification would have resulted in a method that aids in the characterization of cell identity as explicitly taught by Eberwine (Abstract).

14. Claims 59-60, 62-63, 68, and 72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wengel et al (PCT International Publication No. WO 99/14226, published 25 March 1999) in view of Monforte et al (U.S. Patent No. 6,051,378, issued 18 April 2000) in view of Skouv (U.S. Patent No. 6,303,315 B1, issued 16 October 2001) and applied to claim 55 above, and further in view of Gruenert et al (U.S. Patent No. 5,804,383, issued 8 September 1998).

Regarding claims 60, 62-63, and 72, the method of claim 55 is discussed above on pages 4-7. While the method of claim 59 is also discussed above, an alternate interpretation of the method of contacting the sample with a polymerase and at least one nucleotide is taught by Gruenert et al. The method of Gruenert et al comprises generating a plurality of copies via amplification of mRNA using RT-PCR (Abstract). The RT-PCR method involves cycling of the temperature as well as the use of the thermally stable Taq (Is) polymerase (column 25, lines 24-25) and the thermally stable rTh polymerase (column 9, lines 34-50). The RT-PCR method has the added advantage of allowing analysis of gene expression of specific alleles (Abstract).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method as taught by Wengel et al in view of Monforte et al in view of Skouv with the method comprising generation of a plurality of copies of mRNA using temperature cycling and thermostable polymerases as taught Gruenert et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification

Art Unit: 1634

because the modification would have resulted in a method of isolating mRNA using LNA molecules that has the added advantage of allowing analysis of gene expression of specific alleles as explicitly taught by Gruenert et al (Abstract).

Regarding claim 68, the method of claim 59 is discussed above. Neither Wengel et al, Monforte et al, nor Skouv cells stably associated with a solid support.

However, Gruenert et al teach a method of generating a plurality of copies of mRNA by making and amplifying a cDNA copy of the mRNA using reverse transcriptase polymerase chain reaction (Abstract) comprising nucleic acid molecules in cells wherein the cells are stably associated with a solid support; namely, the nucleic acids for the RT-PCR are in cells fixed to a slide then submitted to RT-PCR (column 8; lines 31-60). The fixed cells have the added advantage of allowing destruction of proteins and enzymes that interfere with PCR (column 8, lines 31-50).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method as taught by Wengel et al in view of Monforte et al in view of Skouv by using cells stably associated with a solid support as taught Gruenert et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because the modification would have resulted in a method of detecting eukaryotic mRNA using LNA molecules that has the added advantage of allowing destruction of proteins and enzymes that interfere with PCR as explicitly taught by Gruenert et al (column 8, lines 31-50).

15. Claim 71 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wengel et al (PCT International Publication No. WO 99/14226, published 25 March 1999) in view of Monforte et al (U.S. Patent No. 6,051,378, issued 18 April 2000) in view of Skouv (U.S. Patent No. 6,303,315 B1, issued 16 October 2001) and Eberwine et al (U.S. Patent No. 5,514,545, issued 7 May 1996) as applied to claim 70 above, in further view of Eis et al (Nature Biotechnology, vol. 9, pp. 673-676, (July 2001)).

Art Unit: 1634

Regarding claim 71, the method of claim 70 is discussed above on pages 16-17. Neither Wengel et al, Monforte et al, Skouv, nor Eberwine et al teach cleavage of the LNA; i.e., cleavage of the probe that captures the RNA.

However, Eis et al teach a method of capturing mRNA using invasive cleavage (Figure 1), wherein a probe is cleaved from the mRNA (Figure 1) with the added advantage that invasive cleavage allows direct quantitation of specific RNAs (Title).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method as taught by Wengel et al in view of Monforte et al in view of Skouv in view of Eberwine with cleavage of the capture probe as taught Eis et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because the modification would have resulted in a method of detecting eukaryotic mRNA using LNA molecules that has the added advantage of allowing direct quantitation of specific RNAs as explicitly taught by Eis et al (Title).

16. Claims 77-80 and 140 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wengel et al (PCT International Publication No. WO 99/14226, published 25 March 1999) in view of Monforte et al (U.S. Patent No. 6,051,378, issued 18 April 2000) in view of Skouv (U.S. Patent No. 6,303,315 B1, issued 16 October 2001) and applied to claim 59 above, in further view of Sambrook et al (*Molecular Cloning, A Laboratory Manual*, 2nd ed., Cold Spring Harbor Laboratory Press, NY, pp. 5.58, 8.2, 8.3, 8.60-8.61, and 8.64-8.65 (1989)).

Regarding claims 77-80 and 140, the method of claim 59 is discussed on above on pages 4-7. Neither Wengel et al, Monforte et al, nor Skouv teach DNA polymerase, RNase H and E. coli ligase to generate cDNA.

However, Sambrook et al teach a method of amplifying mRNA comprising adding DNA polymerase, RNase H (pages 8.60-8.61) and E. coli ligase after conversion of polyadenylated mRNA to

Art Unit: 1634

first strand complementary DNA under conditions suitable for generating double stranded complementary DNA (pages 8.64-8.65), and insertion into a cloning vector (page 8.2), with the added benefit of established a comprehensive cDNA library from a small quantity of mRNA (page 8.3, paragraph 1). Sambrook et al also teach an anchor sequence for an RNA polymerase and synthesis of a plurality of mRNA copies, which has the additional added advantage of allowing expression of cloned genes in bacteria (page 5.58, 1st-5th paragraphs).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method as taught by Wengel et al in view of Monforte et al and Skouv with amplification using the steps and enzymes as taught Sambrook et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because the modification would have resulted in establishment of a comprehensive cDNA library from a small quantity of mRNA as well as allowing expression of cloned genes in bacteria explicitly taught by Sambrook et al (page 8.3, paragraph 1 and page 5.58, 1st-5th paragraphs).

17. Claim 90 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wengel et al (PCT International Publication No. WO 99/14226, published 25 March 1999) in view of Monforte et al (U.S. Patent No. 6,051,378, issued 18 April 2000) in view of Skouv (U.S. Patent No. 6,303,315 B1, issued 16 October 2001) and applied to claims 1 and 54 above, in further in view of Gottschling et al (U.S. Patent No. 5,916,752, issued 29 June 1999).

Regarding claim 90, the method of claims 1 and 54 is discussed on above on pages 4-7. While Wengel et al teach detection of Arabidopsis mRNA (page 181, Example 160), neither Wengel et al, Monforte et al, nor Skouv teach yeast RNA.

However, Gottschling et al teach hybridization using yeast RNA with the added advantage that yeast RNA sequences have substantial sequence homology to the human RNA sequences (e.g.,

Art Unit: 1634

telomerase, column 17, line 64-column 18, line 5) and that yeast is a genetically tractable organism directly applicable to mammalian cells (column 23, lines 55-61).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method of detecting RNA as taught by Wengel et al in view of Monforte et al in view of Skouv with yeast RNA as taught by Gottschling et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because the modification would have resulted a method of detecting RNA sequences using LNA wherein the sequences detected have substantial homology to human sequences in a genetically tractable organism directly applicable to mammalian cells as explicitly taught by Gottschling et al (column 17, line 64-column 18, line 5 and column 23, lines 55-61).

18. Claim 93 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wengel et al (PCT International Publication No. WO 99/14226, published 25 March 1999) in view of Monforte et al (U.S. Patent No. 6,051,378, issued 18 April 2000) in view of Skouv (U.S. Patent No. 6,303,315 B1, issued 16 October 2001) and applied to claim 92 above, in further in view of Recker et al (U.S. Patent No. 5,691,153, issued 25 November 1997).

Regarding claim 93, the method of claim 92 is discussed on above on pages 4-7. While Wengel et al teach the target is amplified in a PCR amplification using an additional primer in addition to the first primer (page 195, Example 148), and wherein captured nucleic acids are amplified directly on a surface (page 62, lines 4-10), Wengel et al, Monforte et al, and Skouv are silent with respect to multiplex PCR.

However, Recker et al teach a method of screening nucleic acids (i.e., genome screening) using multiplex PCR with the added advantage that multiplex PCR increases the speed of throughput 10 fold (column 11, lines 20-32).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method comprising the use of PCR as taught by Wengel et al

Art Unit: 1634

in view of Monforte et al in view of Skouv with multiplex PCR as taught by Recker et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because the modification would have resulted a method comprising PCR using LNA having the added advantage that multiplex PCR increases the speed of throughput 10 fold as explicitly taught by Recker et al (column 11, lines 20-32).

19. Claims 114-115 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wengel et al (PCT International Publication No. WO 99/14226, published 25 March 1999) in view of Monforte et al (U.S. Patent No. 6,051,378, issued 18 April 2000) in view of Skouv (U.S. Patent No. 6,303,315 B1, issued 16 October 2001) as applied to claim 110 above, and as evidenced by Sambrook et al *Molecular Cloning, A Laboratory Manual*, 2nd ed., Cold Spring Harbor Laboratory Press, NY, page 7.5 (1989)).

Regarding claims 114-115, the method of claim 110 is discussed above on pages 10-11. Skouv also teaches beta-mercaptoethanol in the lysing and hybridizing buffer (Abstract and column 4, lines 58-67). Sambrook et al define 4M guanidinium thiocyanate and beta-mercaptoethanol as RNase inhibitors (page 7.5). It is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on" (205 USPQ 594, second column, first full paragraph). The inclusion of 4M guanidinium thiocyanate and beta-mercaptoethanol in the lysing buffer taught by Skouv is therefore an RNase inhibitor as required by the claims.

20. Claims 116-117 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wengel et al (PCT International Publication No. WO 99/14226, published 25 March 1999) in view of Monforte et al (U.S. Patent No. 6,051,378, issued 18 April 2000) in view of Skouv (U.S. Patent No. 6,303,315 B1, issued 16

Art Unit: 1634

October 2001) as applied to claim 110 above, and further in view of Alizon et al (U.S. Patent No. 5,310,651, issued 10 May 1994).

Regarding claims 116-117, the method of claim 110 is discussed above on pages 10-11. Neither Wengel et al, Monforte et al, nor Skouv teaches HIV.

However, Alizon et al teach the isolation of genomic RNA from HIV-2 (column 11, lines 1-22), which has consecutively repeating nucleic bases (Figure 1B) with the added advantage that HIV-2 is a second causative agent of AIDS (column 1, lines 58-65).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method comprising the use of PCR as taught by Wengel et al in view of Monforte et al in view of Skouv with detection of HIV as taught by Alizon et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because the modification would have resulted a method of isolating nucleic acids using LNA having the added advantage of detecting a causative agent of AIDS as explicitly taught by Alizon et al (column 1, lines 58-65).

21. Claims 136-137 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wengel et al (PCT International Publication No. WO 99/14226, published 25 March 1999) in view of Monforte et al (U.S. Patent No. 6,051,378, issued 18 April 2000) in view of Skouv (U.S. Patent No. 6,303,315 B1, issued 16 October 2001) and applied to claim 56 above, and further in view of Squirrell et al (U.S. Patent No. 5,837,465, issued 17 November 1998).

Regarding claims 136-137, the method of claim 56 is discussed above on pages 9-10. While Wengel et al also teach detection with probes using chemiluminescence (e.g., an LNA nucleoside has a reporter group [page 9, lines 1-19], wherein the reporter group uses chemiluminescence; page 19, lines 8-20), Wengel et al, Monforte et al, and Skouv do not specifically teach enzyme conjugated probes using chemiluminescence.

Art Unit: 1634

However, Baldwin et al teach nucleic acid probes with chemiluminescent enzymes (e.g. the bioluminescent enzyme luciferase; column 2, lines 14-26) with the added advantage that luciferase allows detection at very low concentrations using simple instruments (column 1, lines 15-20).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method comprising the use chemiluminescence as taught by Wengel et al in view of Monforte et al in view of Skouv with chemiluminescent enzyme as taught by Baldwin et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because the modification would have resulted a method comprising chemiluminescent LNA having the added advantage of allowing detection at very low concentrations using simple instruments as explicitly taught by Baldwin et al (column 1, lines 15-20).

Response to Arguments

22. Applicant's arguments filed 30 November 2006 (i.e., the "Remarks") have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

23. No claim is allowed.

24. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

25. A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing

Art Unit: 1634

date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert T. Crow whose telephone number is (571) 272-1113. The examiner can normally be reached on Monday through Friday from 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Robert T. Crow
Examiner
Art Unit 1634



RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER